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THE ETIOLOGY OF GASTRIC ULCER.[1]

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THE mucous membrane and the deeper structures of the stomach may suffer loss of substance from a variety of processes that may with truth be called ulceration. Thus, ulceration may take place from traumatism, corrosives, scalding fluids; from tuberculosis, syphilis, scurvy, or from serious blood-changes; from extensive burns, from continued pressure, and from other causes that disturb the nutrition of the part.

However, for an ulcer occurring most often in young women, which is usually round; having about it healthy mucous membrane; its margin being abrupt and clean-cut, so that in old cases it has a distinct punched-out appearance (as Rokitansky aptly describes it); generally found alone, but occasionally having one or two companions; located, as a rule, on the posterior wall near the pylorus, and often near the lesser curvature; almost invariably associated with an excessive secretion of hydrochloric acid, and not infrequently with

[1] Read at the meeting of the New York State Medical Association, in New York City, November 17, 1892.

anemia—which is called the "simple," the "solitary," the "round," the "perforating," the "peptic," the "ulcer of Cruveilhier"—for this there has been suggested no cause that is satisfactory, or that answers all important requirements.

It is not to be supposed that one can draw an uninterrupted and perfectly distinct line of separation between true round ulcer and all other forms of gastric ulceration. It is probable that in many instances the processes are so intermingled and confused that even the fullest knowledge of the facts would leave differentiation incomplete; but the fact must, nevertheless, not be lost sight of that in the classical "round ulcer" no theory of etiology so far suggested has proved to be altogether satisfactory. Before discussing this part of the subject, however, let us consider what we know of the causes of gastric ulcer in general.

It is widely believed that the bacilli of tuberculosis passing through the stomach may invade the intestinal mucous membrane, and yet that this organism, while not destroyed by the gastric secretion, has not been shown to be a cause of local trouble in the stomach. Notwithstanding this, there are now reported numerous authenticated instances of tuberculous disease of the stomach,[1] and occasionally extensive ulceration of the mucosa is seen.

Syphilis, according to histologic examinations made by Guozot,[2] has been shown to be a cause of ulcer, and Heller[3] thinks that syphilis plays an important rôle in congenital ulcer, of which a number of cases have been reported.

The disintegration of neoplastic tissue can scarcely be considered as ulceration of the stomach, although it is well known that carcinoma often finds its seat in the place of a preceding ulcer. Albertoni,[4] however, reports a case in which an ulcer was complicated with adenoma of the stomach, and believes that the ulcer resulted from a previous growth of this nature. Turner[5] describes a circumscribed superficial slough of the gastric mucous membrane in a man suffering from pyemia following a fracture of the tibia, and similar cases resulting from septic emboli have at long intervals been reported.

I have seen erosions of the gastric mucosa resulting from extravasations of blood into its substance, in cases of purpura and scurvy; and, according to Wales,[6] such lesions and even distinct ulceration are rarely absent in the latter affection.

Quioroza[7] reports cases of gastric ulcer resulting from dysentery, puerperal septicemia, and typhoid fever, and this author believes that the affection is the direct result of numerous diseases of the body.

An interesting and ingenious explanation of the affection is that given by Wiktorowsky,[8] who maintains that from chronic catarrh the establishment of the chronic interstitial process, up to perforating ulcer of the stomach, is but a continuous chain; but proof of this theory is wanting. Nevertheless, Peter[9] and others hold that round ulcer is the result of a preceding gastritis, and the increased local temperature is mentioned as evidence in that direction. It will be remembered that Cruveilhier[52] held to the inflammatory origin of the disease.

There has been a general acceptance of the views expressed long since by Virchow, that the ulceration follows hemorrhagic erosions resulting from disturbances of the circulation; that "the interruptions of the circulation are for the most part due to morbid conditions of the gastric vessels, and particularly to a hemorrhagic necrosis of the mucous membrane." This hypothesis at once opens a wide avenue for causative factors, and if it were not for certain reasons, hereafter to be mentioned, the attempt to point out a special process in the development of the ulcer described by Cruveilhier would be profitless.

It is most natural and sensible to suppose that, given a hemorrhagic necrosis of the mucosa and the presence of the active gastric juice, the part would become digested, and the typical excavation, so well described by Rokitansky, would appear. This position is substantiated by clinical observations, post-mortem discoveries, and laboratory experiments, so that one cannot deny that ulcers are thus established.

In 294 cases, Berthold[10] found disease of the circulatory apparatus in 170; while Steiner reports such changes in 71 cases out of a total of 110, finding particularly endocarditis, endaortitis, and endarteritis. Thrombosis in various parts was demonstrated 48 times. Litten[11] saw a perforating ulcer with a thrombus in the splenic artery, and Janeway[12] describes a like case in which the ulcer was directly due to a fibrinous plug found in the gastro-epiploic artery. Provost and Cotard produced ulcerative changes in various parts of the

alimentary canal by introducing tobacco seeds into the aorta, and other similar experiments are on record ; and, as might have been expected, Letulle[13] claims to have established the infectious origin of the gastric ulcer.

By experimental means, hemorrhagic necrosis, and, later, ulceration, have by several investigators been produced in dogs. Ritter[14] succeeded by poking a dog's stomach with a cane, and Decker reports like results after feeding to dogs hot gruel. Quincke relates experiments on dogs with gastric fistulæ, in which the mucosa was injured by pinching, excision, or by tying off small portions ; by thermal irritation ; by caustics.

The animals showed no subsequent distress, nor was the digestion impaired, but the ulcers disappeared after from four to twelve days, although the repair was delayed materially by rendering the dogs anemic by bleeding. Von Sohlern[15] thinks that a vegetable diet, by increasing the proportion of potassium salts in the blood, acts against the formation of ulcer, and he mentions the infrequency of the disease among vegetarian people. Silberman[16] repeated these experiments with modifications, and reached the conclusion that ulcer might be caused by arterial anemia, venous hyperemia, portal stasis, circumscribed hemorrhages, or reduced alkalinity, and suggested that the hyperacidity of the gastric juice might depend upon the lowered alkalinity of the blood. Ulcers following blows upon the abdomen in dogs[17] and men[18] are reported, and it is well known that the condition is often seen after severe external burns.[19]

Localized pressure as a cause is mentioned by Rasmussen,[20] and M. Pettit[21] has recently described a fatal case which apparently arose from pressure and rubbing exercised by a bony protuberance on the inside of the lower end of the sternum. Zielinski,[22] of Warsaw, in a recent paper, considers as a cause of gastric ulcer the narrowing of the lumen of the vessels of the stomach from traction made by enteroptosis. Duodenal ulcer not infrequently follows external scalds and burns,[23] and occasionally also the stomach is the seat of like lesions;[19] and severe injuries of various kinds, experimentally made upon animals,[24] have been followed by hemorrhagic necrosis in various parts of the body and in the stomach by ulcers.

Precisely how these changes are brought about is not clear, and it is therefore not surprising that, as Niemeyer has suggested, the nervous system may be a possible factor in the process. Indeed, it was with this in mind that Ebstein made the experiments just alluded to, which were a part of a series of investigations undertaken to show the relation that exists between certain severe injuries and gastric ulcer. Repeating the well-known experiments of Schiff, Ebstein reached somewhat different conclusions; but in the main, both of these investigators agree that injury to certain parts of the central nervous system (optic thalamus, pedunculus cerebri) is competent to establish ulcus ventriculi. Similar results followed a half section of the spinal marrow, and any great and often-repeated irritation of the sensory nerves led to quite uniform changes in the gastric mucosa. Talma[25] was able to produce ulcer

by exciting spasm of the muscular coat of the stomach, through prolonged stimulation of the left vagus. He suggests that the so-commonly present hyperacidity may thus affect the pneumogastric. Apparently this throws light upon the mystery of the relation between external burns and ulcer, and is at any rate highly suggestive of a possible nervous cause operating in cases seen clinically.

Whatever the exciting cause, the lowered alkalinity of the blood on the one hand and the excessive acidity of the gastric juice on the other are generally acknowledged to be active contributing causes. Pavy[26] teaches that the normal alkalinity of the blood successfully opposes ulcer, by preventing the autodigestion of the stomach. This self-preservation on the part of that organ has been shown not to be dependent upon this condition, however, since Samuelson made the blood neutral, and yet the stomach continued to resist its own secretions. This fact throws discredit upon the theory so long and securely taught by Cohnheim,[27] and we must now conclude that in such investigations as these of Silberman's[40] the resulting ulcers were from some other change in the blood besides the mere lowering of its alkalinity. The views of Ewald,[41] that the blood-changes, to be operative, must be such as lower the resistance of the living cell, are more acceptable. There is apparently a close relation existing between the lowered alkalinity and the hyperacidity. The intimacy of the relation pointed out by Pavy has been acknowledged by many. Grime[42] quotes fifty-three cases of ulcer, all of which had hyperacidity, and concludes that it is

due to the preceding chlorosis, and that, with those two conditions present, the slightest injury to the mucous membrane may form the focus of an ulcer.

Riegel[43] and his students insist that the great excess of hydrochloric acid is the invariable accompaniment of gastric ulcer; and while this accords with my own experience, and undoubtedly is true of classical ulcer, there are undoubtedly cases, as shown by Ewald,[44] that are not only without hyperacidity, but even show hypoacidity. The importance of the acidity in delaying the healing, is, as Riegel states,[45] very great, and that it has a marked influence in establishing the lesion is most probable, but the fact remains that ulcer may exist and persist without hydrochloric acid, just as it may appear in those who have not antecedent anemia.

In view of the foregoing facts, necessarily stated incompletely and with brevity, it seems justifiable to suppose that while ulcerative processes dependent upon tuberculosis, syphilis, pyemia, scurvy, and other serious dyscrasias, may proceed in the gastric mucosa, and while simple anemia with lowered alkalinity of the blood assists the process, while hyperacidity of the gastric contents greatly favors the change, there must still be some other as yet unknown cause which in a certain group of cases leads to the necrosis, besides the accidental changes from thrombi and emboli, such as have already been cited above.

The reasons for this claim are: First, that the affection shows itself particularly in adolescence or before middle age, when there is the least proba-

bility of vascular changes; second, that it appears most frequently in women, who are less often subjects of arterial diseases than men; and third, because, with remarkable frequency, the ulcer selects for its site the lesser curvature and posterior wall of the stomach near the pylorus, a portion of the economy that is not often invaded by emboli, and a region of the stomach especially rich in anastomosing vessels. In a large number of cases Buchmüller[46] found over 93 per cent. on the posterior wall near the lesser curvature, and no certain cases under fifteen years. In the Berlin statistics not one case was found under the tenth year, and the greatest number between the twentieth and thirtieth years. It is occasionally congenital,[50] and one altogether exceptional case was found in a man, said to be one hundred and twenty years old.[51] Greiss[47] found from three to five times as many scars in women as in men, and over 90 per cent. appeared on the posterior wall near the lesser curvature; and although many of these appeared in middle, and a few in advanced life, the beginning of the trouble was doubtless in earlier life, as Leube[48] has pointed out. Statistics abound in similar statements, as may be learned by consulting Welch's splendid monograph in Pepper's *System of Medicine*.

From the foregoing facts, namely, the propensity shown by the affection to select a certain site in females, and to appear in early life, has naturally arisen the suggestion that this form of ulcer may take its origin in some unknown but definite neuropathic change—trophic, vasomotor, or both of these. It has seemed to me remarkable that this view has not

gained more adherents, since by no other evident hypothesis can these points in its natural history be explained.

In reflection on the matter, it has occurred to me that somewhat analogous processes are to be witnessed in other parts of the body, and that by using these as illustrations some insight into the pathology of round ulcer may be gained. For instance, the well-known proclivity of herpetic eruptions to attack particular points under especial conditions is brought forward, and attention is called to this common disease, that, depending upon nerve abnormality, is found, not only upon the skin, but upon the mucous membrane of various parts, including the mouth and throat, with a view of asking whether it might not select for its appearance the pyloric extremity of the stomach, and so lead to ulcer.

Again, there is something most suggestive in that extraordinary disease known as idiopathic hematoma auris, which is seen not infrequently in the insane, which invariably appears in the concha, rapidly reaches maturity, and disappears only after destruction of tissue and marked cicatricial deformity. It is interesting to note that the affection has been seen occasionally in those having no mental disease, or other known disability.[40] In a recent paper on this subject, Dr. H. G. Matzinger refers to the complex nerve-supply of the ear, with especial reference to the sympathetics, and concludes that othematoma is a neuropathic affection, seen generally, but not invariably, in those suffering from central nerve disease, in which the sympathetic system is seriously involved. Why might not some similar process have for its local expression the pos-

terior wall, or lesser curvature of the stomach near the pylorus, than which no part of the economy has a more complicated and involved innervation?

One is led also to think of the striking manifestations in that curious affection, Raynaud's disease, with its predilection for the fingers and toes, with its advancing steps of syncope, asphyxia, and necrosis of the parts.

It is not impossible that asphyxia of certain spots of the gastric mucosa may occur from analogous causes, whatever they may be, and the tissue thus put to a disadvantage would be well calculated to suffer erosion from the active gastric juice.

If Morvan's disease is not found to be a phase of syringomyelia, it also might be advanced as an instance of local necrosis, something like that which may appear in the stomach.

A few years ago I saw at the clinic of my colleague, Professor Roswell Park, a case of intense interest, that of a neurotic girl, who had a series of painful and persistent ulcers along the forearm and the leg, following the tracts of certain nerves. The parts bordering the ulcers were uninvolved, and in every way healthy; the ulcers themselves followed the appearance of limited gangrenous spots; they were deep, with abrupt walls, and were exquisitely sensitive. They had for years resisted the treatment by very able men, but those on the arm were permanently cured by a thorough stretching of the external cutaneous nerve, practised by Park. There was something about the appearance of these ulcers that reminded one of the typical round ulcer of Cruveilhier, and it does not seem to me absurd to suppose for the latter a somewhat similar origin.

In concluding this view of the subject, it appears natural to assume that the stomach, like other parts, may suffer loss of substance from a variety of causes; but as regards simple round ulcer, it must have a more precise and definite etiology.

Unquestionably, the impoverished condition of the blood, leading to lowered resistance of "the living cells," and the persistent presence of hyperchlorhydria, must of necessity put the tissues to severe strain—but there is wanted yet another factor. The object of this paper is to suggest that, by the influence of some process analogous to herpes, or to idiopathic hematoma auris, or to Raynaud's disease, or to herpetic gangrene—some distinct and persevering nerve-perturbation — we may best explain the recognized but unaccounted-for feature of the clinical history as to location, age, and sex.

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